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| APPLICATION NO.                                                            | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|----------------------------------------------------------------------------|-------------|----------------------|---------------------|------------------|
| 09/701,013                                                                 | 01/12/2001  | Masaaki Terada       | 0020-4769P          | 4777             |
| 2292                                                                       | 7590        | 12/19/2003           | EXAMINER            |                  |
| BIRCH STEWART KOLASCH & BIRCH<br>PO BOX 747<br>FALLS CHURCH, VA 22040-0747 |             |                      | CHEN, SHIN LIN      |                  |
|                                                                            |             |                      | ART UNIT            | PAPER NUMBER     |
|                                                                            |             |                      | 1632                |                  |

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/701,013

Applicant(s)

TERADA ET AL.

Examiner

Shin-Lin Chen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 24 September 2003 and 13 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 34-37 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 37 is/are allowed.
- 6) ☒ Claim(s) 34-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Upon further consideration of the present invention, the finality of the Official action mailed 3-14-03 (Paper No. 12) has been withdrawn.

Applicants' amendments filed 9-24-03 and 11-13-03 have been entered. Claims 1-33 have been canceled. Claim 37 has been added. Claims 34-37 are pending and under consideration.

#### ***Claim Rejections - 35 USC § 103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Manis et al., 1982 (US Patent No. 4,332,900) in view of Szoka et al., 1996 (WO 96/40265).

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Claims 34 and 36 are directed to a stable gene formulation lyophilized from an aqueous solution comprising a closed circular plasmid vector containing a desired gene, and a citric acid, tartaric acid or a mixture thereof. Claim 36 specifies the formulation further comprises a cationic lipid, a cationic polymer, or a hydrophobic polymer.

It should be noted that the intended use of a product claim does not carry weight in the 35 U.S.C. 103(a) rejection.

Manis teaches preparing covalently closed circular plasmid DNA PUC6 by cesium chloride centrifugation, isopropyl alcohol extraction, and dialyzing the aqueous phase against buffer containing sodium citrate to purify plasmid PUC6 (e.g. column 6). Manis teaches DNA methodology to prepare a plasmid containing a desired gene, such as an insulin gene, and the use of the resulting plasmid to transform a host microbe to produce the desired insulin (e.g. abstract).

Manis does not teach adding a cationic lipid, a cationic polymer, or a hydrophobic polymer to the DNA preparation, or lyophilizing the DNA solution.

Szoka teaches that polynucleotide complexes can be stabilized by adding a cryoprotectant compound, such as carbohydrate including lactose, sucrose, glucose, mannitol, sorbitol, trehalose. The polynucleotide complexes could be plasmid DNA, polynucleotide associated with a cationic lipid, or a polynucleotide associated with a liposome or lipidic particle. Szoka teaches lyophilization of the polynucleotide complexes and the lyophilized formulation may be stored for extended period of time and then rehydrate prior to use for gene delivery (e.g. abstract, p. 1, 24).

It would have been obvious for one of ordinary skill at the time of the invention to prepare a stable gene formulation comprising a closed circular plasmid DNA, citric acid, tartaric

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acid or mixture thereof, or further comprising a cationic lipid, a cationic polymer, or a hydrophobic polymer because Manis teaches preparing covalently closed circular plasmid DNA solution containing citric acid and Szoka teaches stabilizing polynucleotide complexes having a cationic lipid, a liposome or lipidic particle by adding cryoprotectant compound and lyophilizing said polynucleotide complex. It was well known in the art that plasmid DNA has three different forms, i.e. closed circular (supercoiled DNA), relaxed, and linear DNAs, and a plasmid DNA preparation usually contains closed circular (supercoiled DNA) and relaxed DNAs. Therefore, the plasmid DNA taught by Szoka would comprise closed circular plasmid vector. Further, it was well known in the art to lyophilize DNA solution during the purification of a plasmid DNA and dispense the plasmid DNA in appropriate volume of water or buffer solution. Thus, it also would have been obvious for one of ordinary skill in the art to lyophilize the dialyzed plasmid DNA solution as taught by Manis.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to store plasmid DNA for extended period of time as taught by Szoka and to prepare plasmid DNA solution for gene delivery or transfection of a host cell as taught by Szoka and Manis with reasonable expectation of success.

4. Claims 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Manis et al., 1982 (US Patent No. 4,332,900) in view of Szoka et al., 1996 (WO 96/40265) and further in view of Fujioka et al., 1993 (US Patent No. 5,236,704) and Bonadio et al., 1998 (US Patent 5,763,416 A).

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Claims 34-36 are directed to a stable gene formulation lyophilized from an aqueous solution comprising a closed circular plasmid vector containing a desired gene, and a citric acid, tartaric acid or a mixture thereof. Claim 35 specifies the formulation further comprises an atelocollagen. Claim 36 specifies the formulation further comprises a cationic lipid, a cationic polymer, or a hydrophobic polymer.

The teachings of Manis and Szoka are as discussed above. Manis and Szoka do not teach adding atelocollagen into the gene formulation.

Fujioka teaches preparation of a controlled release formulation by lyophilizing a mixture of an active ingredient such as protein or peptide, collagen such as atelocollagen and an appropriate amount of an acidic compound having one or more carboxylic groups, such as citric acid and tartaric acid, as an additive, pulverizing the resulting solid product, and compression-molding the pulverized product in a template or charging the above-mentioned mixture in a template and condensing or drying the mixture, so as to obtain the formulation in a solid form, whereby any formulation, having a desired size and shape suitable for a particular administration route and a particular position to be applied can be obtained. Fujioka also teaches preparation of an aqueous solution containing 2 w/w% atelocollagen, an acidic compound and a growth hormone releasing factor, wherein the aqueous solution is lyophilized to prepare a column-shaped formulation which is administered subcutaneously to rats (e.g. column 7, 8, 9). Fujioka teaches sustained release formulations, which release an active ingredient over a long period of time, are useful for the increase of therapeutical effects due to prolonged retention of an active ingredient over effective level in the blood, the decrease of side-effects by reducing the maximal

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blood level of the active ingredient, simplification of administration methods and a reduction in a patient's level of pain due to a decrease of administration frequency (e.g. column 1).

Bonadio teaches a composition comprising a nucleic acid segment in association with a structural bone-compatible matrix, wherein said nucleic acid segment is a DNA molecule, RNA molecule, or antisense nucleic acid molecule and said nucleic acid segment can be inserted within genomes of recombinant viruses, wherein said matrix is a collagen preparation, hydroxyapatite, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix (e.g. column 4, 5, 22, 66 and 68). Bonadio also teaches a method for transferring a nucleic acid segment into bone progenitor cells located within bone progenitor tissue comprising contacting said tissue with a composition comprising a nucleic acid and a structural bone-compatible matrix, such as a collagen preparation, wherein said nucleic acid expresses transcriptional or translational products in said cells (e.g. column 63-65).

It would have been obvious for one of ordinary skill in the art at the time the invention to add atelocollagen in a DNA preparation because Bonadio teaches delivering a compositions comprising collagen and nucleic acids to cells and atelocollagen is an enzyme digestive product of collagen and is a derivative of collagen.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to store plasmid DNA for extended period of time as taught by Szoka or to deliver a closed circular plasmid vector containing a gene in a controlled release formulation which releases the vector over a long period of time for gene transfer to the cells of a subject as taught by Fujioka and Bonadio with reasonable expectation of success.

***Conclusion***

Claims 34-36 are rejected. Claim 37 is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. Due to the move of USPTO to new site in Alexandria, Virginia, examiner's telephone number will be changed to (571) 272-0726 **after January 12, 2004**. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.



Shin-Lin Chen, Ph.D.